REMARKS

Reconsideration of this application is respectfully requested.

Applicants hereby bring to the Examiner's attention copending application Serial No. 09/571,355, filed May 15, 2000, directed to "Aromatase Inhibitors and Monoclonal Antibodies As AntiTumor Agents." Similarities may exist between the claims of the copending application and the instant application. At least one Office Action has issued in the related application.

Claims 24-47 were pending in this application. Claims 25-27, 29, 37-39, 41, and 44-45 have been canceled without prejudice to the filing of continuing applications. Claims 24, 28, 34-36, 40, 42-43, and 46-47 have been amended and new claims 48-49 added. Support for the new and amended claims can be found, for example, in the canceled claims. Claims 24, 28, 30-36, 40, 42-43, and 46-49 are now pending in this application. No new matter has been added to the application as a result of the present amendment.

Turning to the Office Action, the following rejections are asserted: claims 24-34 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification; claims 24-26, 29, 34-38, 41, and 46 stand rejected also under § 112, as not being enabled; claims 25, 27, 31, 34, 37, 39, 44-45, and 47 stand rejected under § 112, second paragraph, as being indefinite; and claims 24-47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Am. J. Clin. Oncol,* 11(5), 528-534 (1988) ("Grem"), U.S. Patent 4,871,528 ("Tognella"), and U.S. Patent 5,795,909 ("Shashoua"). Each of these rejections is addressed below.

First Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 24-34 stand rejected as containing subject matter not described in the specification. Under the present amendment, the alleged new matter has been deleted from the

claims. Thus, without conceding the correctness of the rejection, Applicants submit that the § 112 rejection of claims 24-34 is now moot. Withdrawal of the rejection is respectfully requested.

Second Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 24-26, 29, 34-38, 41, and 46 stand rejected as not being enabled. The Examiner contends that the specification does not provide enablement for all compounds having antineoplastic function and all compounds for inhibiting aromatase. See Office Action, page 4. Applicants respectfully traverse this rejection. However, in order to expedite prosecution of this application, Applicants have amended the claims to remove the grounds for rejection. In particular, the claims have been amended to recite specific antineoplastic agents and aromatase inhibitors. Thus withdrawal of the § 112 rejection of claims 24-26, 29, 34-38, 41, and 46 is respectfully requested.

Second Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 25, 27, 31, 34, 37, 39, 44-45, and 47 stand rejected as being indefinite.

Claims 25, 27, 37, and 39 were rejected, with the Examiner alleging that the claims contain the trademark names YM 511, PNU 159548, and PNU 166148, and are thus of uncertain claim scope. Applicants respectfully submit that YM 511, PNU 159548, and PNU 166148 are recognized in the art as names referring to specific compounds. A person of ordinary skill in the art would know, or could readily determine, the structure of each of these compounds. Applicants have amended the claims to include the more common chemical names for these compounds, as found in the references cited in the specification, on page 2, line 16, and page 3, lines 10-11 and lines 15-16. Thus, YM 511 has been replaced with "4-[(4-bromobenzyl)(4-cyanophenyl)amino]-4H-1,2,4-triazole" (see Chem Pharm Bull (Tokyo), 1996 Oct;44(10):1871-9, providing this chemical name for YM 511); PNU 159548 has been replaced with "4-

demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyldaunorubicin;" and PNU 166148 has been replaced with "a polymeric derivative of camptothecin designated PNU 166148."

Claims 44-45 were rejected as reciting a broad range and a narrow range within the same claim. The claims have been canceled and reintroduced as claims 48-49. The new claims overcome the rejection.

Claims 31 and 47 stand rejected as not being supported by sufficient antecedent basis. The claims, as amended, overcome this rejection.

Claim 34 was rejected as indefinite. The claim has been amended to overcome this rejection.

As a result of the above amendments and comments, Applicants submit that all grounds for rejection under 35 U.S.C. § 112, second paragraph, have been removed. Accordingly, withdrawal of the § 112 rejection of claims 25, 27, 31, 34, 37, 39, 44-45, and 47 is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 24-47 stand rejected as being unpatentable over Grem, Tognella, and Shashoua. The Examiner contends: that Grem discloses the combination of the antineoplastic agents cyclophosphamide, doxorubicin, and 5-fluorouracil, with the aromatase inhibitor aminogluthetimide for the treatment of breast cancer; that Tognella discloses that certain anti-tumor agents alone or in combination with other anti-tumor agents, are useful for treating breast cancer; and that Shashoua discloses that certain antineoplastic agents and certain aromatase inhibitors are known to be useful in the treatment of cancer. The Examiner, relying on *In re Kerkhoven*, concludes that it would have been *prima facie* obvious to combine two active composition components into a single composition to form a third composition useful for the

same purpose. See Office Action, page 13, citing *In re Kerkhoven,* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Applicants respectfully traverse this rejection.

In re Kerkhoven is inapplicable where an applicant discovers that the combination of two compositions provides a third composition having *unexpected characteristics*. See MPEP 716.02(a), citing *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989). Further, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully submit that one skilled in the art would not have arrived at Applicants' claimed invention based on the teachings of Grem, Tognella, and Shashoua, either alone or in combination.

The inventors of the instant application have surprisingly discovered that "the therapeutic effect of a chemotherapeutic cytotoxic (antineoplastic) agent is significantly improved and side effects decreased by co-administering it with an aromatase inhibitor antitumor agent." Specification, page 4, lines 15-18. The results of the inventors' pharmacology studies reveal that the combination of the two agents provides a superadditive therapeutic effect, i.e., an effect "which is greater than the sum of the actions of the individual components." See specification, page 5, lines 21-23 and pages 7-10. Thus, the inventors observed: "when the two drugs were combined a super additive effect was observed, and almost all tumor regressed (92%). Also the appearance of new tumors was completely suppressed (0 tumor per rat) only with the

combination." Specification, page 9, lines 18-21. Applicants respectfully submit that *In re Kerkhoven* is inapplicable to the claimed invention because of the unexpected results of the invention. These unexpected results are not disclosed and are not suggested by the cited references.

Grem relates to a phase II study designed to determine whether the combination of cyclophosphamide, doxorubicin and 5-fluoracil, together with aminoglutethimide with hydrocortisone supplementation, can be safely administered with acceptable toxicity to a breast cancer patient. Grem, page 529, left column. Although Grem concludes that the drugs can be safely combined, Grem makes no finding of a superadditive effect resulting from the combination. In fact, Grem concludes that the efficacy of the combination "is comparable to that expected with other doxorubicin-based regimens" and that "the overall response rate is similar to that observed on prior . . . trials with cyclophosphamide, doxorubicin, and 5-fluorouracil." See Grem, page 529, left column, and abstract. Thus Grem concludes that the response rate of the combination composition is similar to the response rate of the antineoplastic agents alone. It follows, therefore, that Grem teaches away from a superadditive effect resulting from the combination of antineoplastic agents and aromatase inhibitors, as presently claimed.

Tognella describes compositions containing antitumor agents and reduced glutathione, which are said to have anti-tumor activity. Tognella, col. 1, lines 11-15. Tognelli, does not disclose or suggest a combination therapy that includes an aromatase inhibitor, as presently claimed. Thus, the reference cannot support a *prima facie* obviousness rejection.

Shashoua relates to conjugates of pharmaceutical agents with highly lipophilic groups, which are said to have a different selectivity for various tissues than the unconjugated pharmaceutical agents. Shashoua, col. 3, lines 52-59. A myriad of categories of pharmaceutical agents are said to be conjugateable, including various antineoplastic agents and various

aromatase inhibitors. Shashoua, col. 4, line 21 to col. 5, line 19, and col. 31. Shashoua does not disclose any compositions that include the combination of an antineoplastic agent and an aromatase inhibitor. That antineoplastic agents and aromatase inhibitors may be independently useful for treating cancer is already known. See Applicants' specification, Background of the invention. The combination of these agents to provide a composition having a superadditive effect however, as presently claimed, is neither taught nor suggested by the prior. Thus the reference lacks the suggestion or motivation required for a showing of *prima facie* obviousness.

In summary, Applicants respectfully submit that neither Tognella and Shashoua teach or suggest the claimed invention. In addition, Grem teaches away from the claimed superadditive effect resulting from the combination of antineoplastic agents and aromatase inhibitors. Thus a person of ordinary skill in the art would not be motivated to arrive at Applicants' invention based on the cited references. For at least these reasons, Grem, Tognella, and Shashoua cannot support a *prima facie* obviousness rejection of the claims. Accordingly, withdrawal of the § 103 rejection of claims 24-47 is respectfully requested.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. Applicants urge the Examiner to contact the Applicants' undersigned representative at (312)913-0001 if the Examiner believes that this would expedite prosecution of this application.

Respectfully submitted,

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